

# Off-label medication use in pediatrics and associated factors at public hospitals in east Gojjam zone, Ethiopia

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## Abstract

**Objective:** Due to a lack of appropriate pediatric preparations, health providers frequently use adult formulations in an off-label manner. This study aimed to assess pediatric off-label medication use patterns and associated factors in East Gojjam, Ethiopia.

**Methods:** Institutional-based cross-sectional study was conducted from December 2020 to June 2021 at three randomly selected hospitals. Data were collected by using self-structured questionnaires and a data abstraction checklist from health care workers and prescriptions, respectively. The collected data were analyzed using SPSS version 25. Logistic regression analysis was used to assess the association between independent and dependent variables.

**Results:** A total of 285 eligible health professionals from the pediatric unit and pharmacies, and 1,800 eligible prescriptions were involved in the study. The response rate of healthcare workers was 94.37%. Around 74.4% of professionals had good knowledge about off-label medication. Only 8% of participants had taken training on pediatric off-label medications. Of all prescriptions, 27.6% of them have contained at least one off-label medication. Phenobarbitone (16.1%) and phenytoin (12.7%) were the most frequently prescribed off-label medication. In all, 496 (27.6%) prescriptions contained off-label drugs in the form of overdose, cutting adult tablets into small portions, and formulating tablets/capsules into solution. Lack of information on off-label prescribing, shortage of pediatric drugs, and suitable dosage forms showed significant association with off-label prescribing with  $p$ -value  $< 0.001$ .

**Conclusion:** Almost one-third of pediatric prescriptions contained off-label medication. Only a small number of healthcare workers had taken training on pediatric off-label medications. Lack of sufficient information on risks of off-label medication, shortage of pediatric medication, and suitable pediatric dosage forms were associated with the use of off-label medication compared to non-use. Further research should be done on the long-term effects associated with off-label prescribing in pediatrics to assess whether the potential risks are balanced with the therapeutical benefit.

## Keywords

Off-label use, pediatric medication, associated factors, Ethiopia

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## Introduction

Age-appropriate formulations are frequently required when developing medications for children. Pediatric drug development is fraught with difficulties due to the complicated scientific and ethical requirements for pediatric studies, a lack of financial assistance, high formulation costs, and a tiny and fragmented market.<sup>1</sup> Because of these challenges, only a few studies are attempting to produce drugs that meet the needs of children. Due to these obstacles (a lack of appropriate pediatric formulations), health care providers regularly provide adult drugs to children in an off-label manner.<sup>2,3</sup>

The use of licensed pharmaceutical medications for unauthorized indication, an unapproved age group, dosage form, dose, or route of administration is known as off-label medication. Off-label prescribing remains an important public

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health issue for neonates, infants, children, and adolescents, especially for pediatric patients with rare diseases. For patients with rare diseases, the majority of medications have no or limited information in the labeling for pediatric use.<sup>4</sup> Off-label use is possible with both prescription and over-the-counter (OTC) medicines, while most studies on off-label use focus on prescription drugs.<sup>5,6</sup> Cutting tablets, segmenting transdermal patches, forming a solution or suspension using solid dosage forms, and diluting liquid dosage forms are all methods used to give off-label medications.<sup>2</sup> Off-label prescribing is ubiquitous in all age groups, although it is more prevalent in pediatric populations.<sup>2,7</sup> Off-label medication of adult formulations may expose pediatrics to potentially dangerous excipients in addition to the active components (drugs). This could be related to children's physiological immaturity, which makes them extremely susceptible to chemicals, including excipients.<sup>8-10</sup> As a result, before using excipients in a pediatric pharmaceutical preparation, a thorough safety review of the excipients is required, referring to available safety data from adult humans and animals as well as safety data from pediatric use and juvenile toxicity studies.<sup>11,12</sup>

Healthcare professionals are increasingly concerned about the safety and efficacy of off-label prescribing in children, owing to a lack of long-term safety and efficacy data in this vulnerable population.<sup>13,14</sup> Off-label medications have been linked to severe adverse drug reactions (ADR) and treatment failure in children; as a result, these drugs should only be provided when the benefits outweigh the risks.<sup>15-17</sup> Off-label medications commonly result in major ADR, treatment failure, and even death in children, according to a 2017 World Health Organization (WHO) report on pediatrics health. To decrease the adverse effects associated with off-label pediatric medications, it is critical to quantify the occurrence of off-label prescribing practice as well as examine the awareness and associated factors of health professionals that work with pediatric units. It is critical to establish the scope of pediatric off-label medications and associated factors among health professionals as a baseline for providing training to concerned health care personnel.<sup>10,18</sup>

To present, only a small amount of information has been published about the practices of various healthcare professionals around the world, and little information has been published about off-label pediatric medications and associated risks in Ethiopia. There are two studies in Gondar and Mekelle University, Ethiopia, only on neonatal patients before 8 years. These studies also do not include the associated factors that lead to off-label medications. As a result, the purpose of this study was to assess the off-label medication use in pediatrics and associated factors at selected public hospitals in east Gojjam, Ethiopia.

## Materials and method

### Study area

The study was conducted in hospitals of East Gojjam zone. East Gojjam Zone is one of the zones of the Amhara region,

and according to the last population census, the zone has a population of 2,153,937. The administrative town of the zone is Debre Markos which is located 300 km Northwest of Addis Ababa. The zone has 10 hospitals. The study was conducted in three randomly selected hospitals including Debre Markos comprehensive specialized hospital, Shegaw Mota general hospital, and Mertu-lemariam primary hospitals located in the East Gojjam zone. In the three selected hospitals, there are 302 healthcare workers who work in pediatric units.

### Study design and study period

An institutional-based cross-sectional study was carried out in three randomly selected hospitals. The study was done between 1 December 2020 and June 2021. The sociodemographic characteristics, knowledge, and perceived barriers data were collected from health care workers who work in pediatric and pharmacy units (pediatricians, general practitioners, nurses, midwives, and pharmacy professionals).

### Ethical approval

Ethical clearance was obtained from Debre Markos University, College of Health Sciences, ethical review committee with reference number HSC/R/C/Ser/Co/210/11/13. After obtaining an official letter from the college, a permission letter was provided to all selected hospitals before the data collection. The study participants were informed about the objective, rationale, and expected outcomes of the study, and written consent was obtained for guaranteeing their choice of participation or refusal.

### Operational definitions

Good knowledge: those respondents who answer 50% and above of knowledge questions.

Poor knowledge: those respondents who answer less than 50% of knowledge questions.<sup>19</sup>

### Source population

All pediatricians, general practitioners, nurses, midwives, and pharmacy professionals who work in East Gojjam zone hospitals were the source population. For prescription review, all pediatric prescriptions prescribed in the last year before the study period in East Gojjam zone hospitals were used as the source population.

### Study population

Pediatricians, general practitioners, nurses, midwives, and all who work in the pediatrics unit and all pharmacy professionals in the selected hospitals who worked in the last year before the study period were the study population. For prescription review, pediatric prescriptions prescribed in the last

year before the study period in the selected hospitals were used as the study population.

### *Inclusion and exclusion criteria*

Pediatricians, general practitioners (GPs), nurses, midwives, and pharmacists who were available during the study period and who were working in the last year before the study period in the selected hospitals were included. And all pediatric prescription papers that have complete patient and drug information were included in the study. Pediatric prescriptions having only medical supplies and reagents were excluded from the study. Trainees were not included in the study. Blood products, contrast, intravenous fluids, electrolyte replacements, and external products were not included in the data extraction.

### *Sample size and sampling technique*

Three randomly selected hospitals including Debre Markos comprehensive specialized hospital (DMCSH), Shegaw Mota general hospital (SMGH), and Mertu-lemariam primary hospital (MLPH) located in the East Gojjam zone were included in the study. There are 302 health care workers who work in the pediatrics unit of study hospitals. Of these, 17 healthcare workers were excluded from the study as they were not available in the study area during data collection. Finally, 285 (171 from DMCSH, 76 from SMGH, and 38 from MLPH) health care workers (pediatricians, GPs, pediatric nurses, midwives, and pharmacy professionals) in the selected hospitals were included in the study. To determine the sample size of pediatric prescriptions, 1,800 prescriptions (600 from each hospital) were selected randomly as per WHO recommendation.<sup>20</sup>

### *Variables of the study*

The dependent variable of this study was off-label pediatric medication prevalence. The independent variables include sociodemographic characteristics of health professionals, knowledge of health professionals, such as perceived barriers, lack of guidelines (internal protocol), shortage of drugs for pediatrics, shortage of suitable drug formulation for pediatrics, and availability of functional drug information center (DIC).

### *Data collection tools and methods*

Data were collected using a structured self-administered questionnaire containing sociodemographic information, knowledge of health professionals about off-label medications, and the barriers which lead to these medications. The data from prescriptions were collected using a data abstraction checklist. The validity and reliability of the data collection tools were checked by the pretest mechanism. The questionnaire and the

data abstraction checklist were adapted by reviewing several kinds of literature on similar studies and guidelines regarding off-label pediatric medication.<sup>10,15,16</sup>

### *Data quality assurance*

To maintain the quality of the data, data collectors and supervisors were trained in data collection procedures. Before actual data collection, tools were checked for clarity and comprehensiveness by an expert as well as pretest was done on 10% of the total sample, thereby possible adjustment and modification was made to the tools. The collected data were then reviewed and checked for completeness and consistency by the principal investigators.

### *Statistical analysis*

Data were checked for completeness and the consistencies of questionnaires were also checked, coded data, and then data entry was made using Epi data 3.1 Software. Then, the data were exported to the SPSS version 25 for further analysis. Before analysis, data were cleaned for possible errors, and then data were presented in frequency, proportions, and summary statistics to describe the factors under study. Bivariable and multivariable logistic regression analyses were used to assess the association between the independent variable and the dependent variable of the study. p-values <0.05 considered to be statistically significant in binary logistic regression were included in the multivariable logistic regression analysis. To determine the off-label status of the prescribed drugs, we used the Ethiopian drug formulary, British drug formulary, and drug information leaflet as a standard.

## **Results**

### *Sociodemographic characteristics of the participants*

In this study, a total of 285 eligible health professionals who worked in the pediatrics and pharmacy units were involved. Pediatricians, general practitioners, nurses, midwives, and pharmacy professionals participated, of which 151 (53.0%) were nurses. Only 4 (1.4%) of pediatrics specialists participated (Table 1).

### *Knowledge about off-label medications*

Most (79.65%) participants were aware of the toxicity and safety profile of medicines in pediatrics. One hundred four (36.5%) participants were not aware of the alternative off-label medications when approved medications are not available. About 240 (84.2%) participants were aware of double-checking dose calculation for pediatric off-label medication. One hundred five (36.84%) respondents were not aware about asking for consent from parents is always

**Table 1.** Distribution of health professionals who participated in the study (N = 285).

| Profession             | Qualification |        |        |            |               | Sex  |        | Total | %    |
|------------------------|---------------|--------|--------|------------|---------------|------|--------|-------|------|
|                        | Diploma       | Degree | Master | Specialist | Subspecialist | Male | Female |       |      |
| Pediatricians          | –             | –      | –      | 4          | –             | 4    | –      | 4     | 1.4  |
| General Practitioners  | –             | 21     | –      | –          | –             | 17   | 4      | 21    | 7.4  |
| Nurses                 | 42            | 98     | 11     | –          | –             | 55   | 96     | 151   | 53.0 |
| Midwives               | 7             | 31     | 5      | –          | –             | 34   | 9      | 43    | 15.1 |
| Pharmacy Professionals | 39            | 25     | 2      | –          | –             | 47   | 19     | 66    | 23.2 |
| Total                  |               |        |        |            |               |      |        | 285   | 100  |

**Table 2.** Perceived barriers to using off-label medications in pediatrics (N = 285).

| Perceived barriers  | Yes       |       | No        |        |
|---|-----------|-------|-----------|--------|
|   | Frequency | %     | Frequency | %      |
| Access to information about the risk/benefit of off-label pediatric off-label drug use in hospitals | 86        | 30.18 | 199       | 69.82  |
| Availability of guidelines for off-label/unlicensed drug use in hospitals                           | 0         | 0.00  | 285       | 100.00 |
| Access to updated drug formulary in hospitals   | 64        | 22.45 | 221       | 77.55  |
| Availability of functional Drug information center in hospitals                                     | 246       | 86.30 | 39        | 13.70  |
| Availability of pediatric medications in hospitals  | 49        | 17.20 | 236       | 82.80  |
| Availability of suitable pediatric dosage forms for prescribed medications in hospitals             | 67        | 23.50 | 218       | 76.50  |
| Have you taken training related to pediatric off-label medication prevalence?                       | 23        | 8.00  | 262       | 92.00  |

mandatory to prescribe/dispense off-label pediatric medication. Two hundred twelve (74.38%) participants had good knowledge, and 73 (25.62%) participants had poor knowledge regarding the use of pediatric off-label medication.

### Perceived barriers to using off-label medications

All participants were responded that there is no available guideline to use pediatric off-label medication. In all, only 23 (8%) of health professionals were taken training on pediatric off-label medication-related issues. Only 49 (17.2%) participants responded that all pediatric medications are available in their health facilities (Table 2).

### Off-label medication utilization pattern

Data were collected from a total of 1800 eligible prescriptions prescribed for pediatrics in outpatient and inpatient pharmacies of Debre Markos Comprehensive specialized hospital, Motta district hospital, and Mertu-lemariam district hospital. Of all pediatric prescriptions, 496 (27.6%) prescriptions contained at least 1 off-label medication according to Ethiopian Formulary, British National Formulary (BNF), and drug information leaflet as shown in Figure 1.

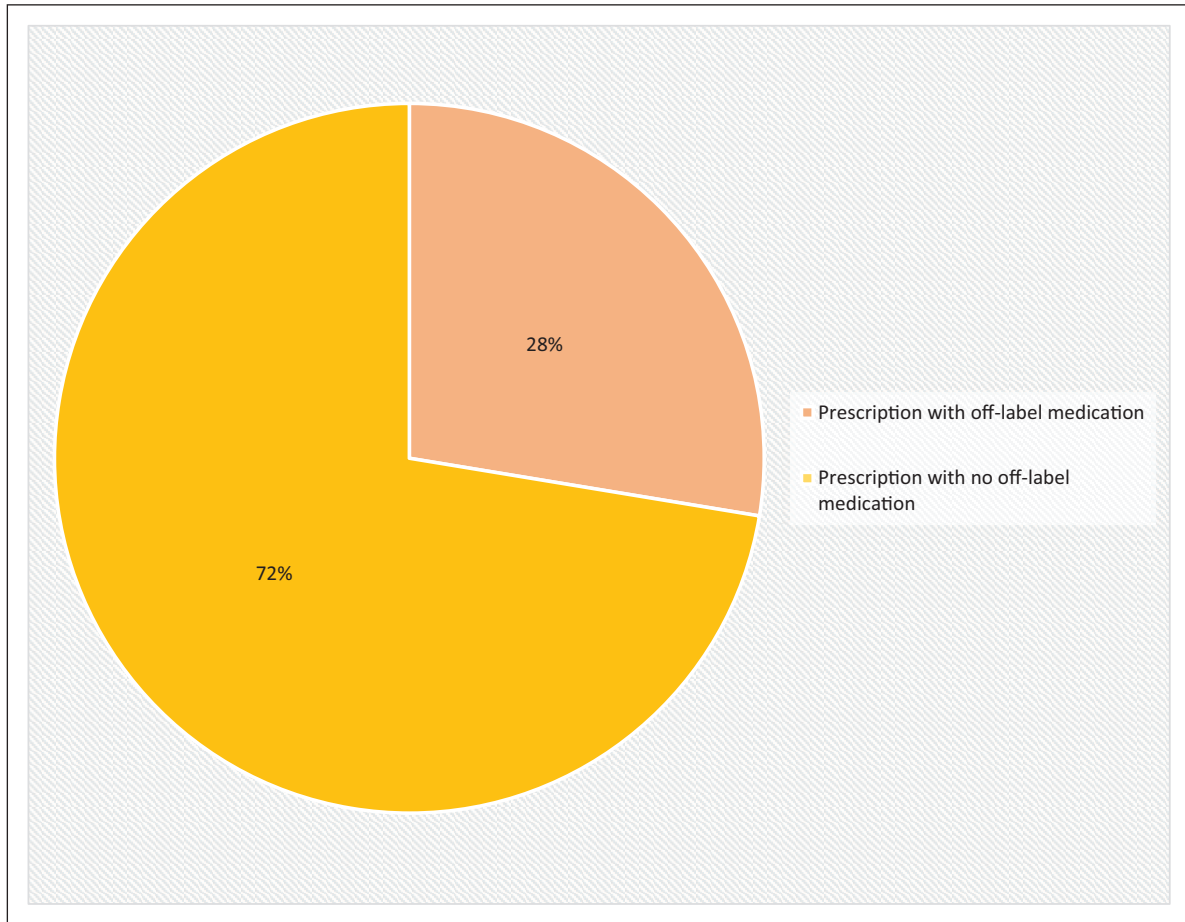
Of total prescribed off-label pediatric medication, the highest proportions (32.5%) were prescribed from the central nervous system (CNS) drug groups. The most frequently prescribed pediatric drugs are phenobarbitone and phenytoin that accounted for 16.1% and 12.7%, respectively (Table 3).

Of all prescriptions that contain off-label medications, prescriptions with overdose medication, cutting adult tablets into small portions, and formulating tablets/capsules in the form of solutions and suspensions were the most frequently (27.2%) prescribed (Figure 2).

According to the WHO age category, pediatrics is divided into three, that is, new term infants (0 to 23 days), infants (>28 days to 23 months), and children (2 to 12 years). Of all off-label prescribed medications, 401 (80.8%) medications were prescribed to age groups of pediatrics from 2 to 12 years (Figure 3).

### Factors associated with off-label medication use

In this study, bivariable logistic regression was done for the gender of health professionals, training, information access about off-label medication, availability guidelines, availability of updated formulary, presence of functional DIC, availability of pediatric medication, and availability of suitable pediatric dosage to assess association with off-label medication use. But only lack of access to information about off-label medication, shortage of pediatric drug availability, and lack of suitable pediatric dosage form showed a significant association with off-label medication use with both bivariable and multivariable logistic regression. Health professionals with a lack of information access about off-label medication were 11.97 times more likely to use pediatric off-label medications compared to those with information access (adjusted odds ratio [AOR]=11.968, 95% confidence interval [CI]: 5.648–25.368).



**Figure 1.** Off-label prescription prevalence (N = 1800).

Health professionals with a lack of pediatric medication in their facilities were 4.68 times more likely to use pediatric off-label medications compared to those with sufficient pediatric medication (AOR=4.683, 95% CI: 2.113–10.379). Health professionals with a lack of suitable pediatric dosage forms were 46.7 times more likely to use pediatric off-label medications than those with access to suitable dosage forms of pediatric medications (AOR=46.725, 95% CI: 31.483–69.347; Table 4).

## Discussion

This study used a large representative sample of prescriptions and health professionals from hospitals in East Gojjam Zone, Ethiopia, to analyze the off-label pediatric prescribing prevalence and associated factors. The study will provide a significant contribution because it is the first attempt to gather information on off-label prescribing prevalence and associated factors. Most of the participants in this survey were aware of the toxicity and safety profile of drugs used in children. The majority (74.38%) of the participants had a high understanding of pediatric off-label medicine, while 25.62% of them had poor knowledge. This result is similar to

one obtained in China, where the majority of respondents (84.5%) stated that they were aware of off-label pediatric medication.<sup>10</sup> In this study, all health professionals said that there was no internal guideline (protocol) that focused on pediatric off-label medication. This conclusion contrasts with the findings of a study conducted in China and India, which revealed that nearly half of the participating institutions had developed internal policies for off-label medication.<sup>10,21</sup> This large disparity in results could be attributed to a lower percentage of higher level healthcare practitioners with clinical knowledge. We might be able to learn from China how to offer safe and effective drugs to children. Only 23 (8%) of health professionals were trained in pediatric off-label medication-related training.

In this study, almost one-third (27.6%) of all prescriptions prescribed in hospitals contained at least one off-label medicine. This result is similar to the 31.7% off-label pediatric prescribing frequency found in an institutional-based, cross-sectional survey conducted in Brazilian hospitals.<sup>22,23</sup> The absence of appropriate pediatric medications and dosage forms may be the cause of frequent off-label prescribing. However, when compared to other study findings from around the world, this study's outcome was lower, with

**Table 3.** Prescribed pediatric off-label drugs (N=496).

| Drug name              | Frequency | %     |
|------------------------|-----------|-------|
| Cephalexin             | 25        | 5.0   |
| Zinc                   | 23        | 4.6   |
| Cloxacillin            | 62        | 12.5  |
| Paracetamol            | 27        | 5.4   |
| Amoxicillin            | 66        | 13.3  |
| Albendazole            | 16        | 3.2   |
| Benzathine Pen         | 6         | 1.2   |
| Furosemide             | 22        | 4.4   |
| Ceftriaxone            | 17        | 3.4   |
| Metronidazole          | 5         | 1.0   |
| Hydrocortisone         | 1         | 0.2   |
| Salbutamol             | 1         | 0.2   |
| Tramadol               | 1         | 0.2   |
| Azithromycin           | 3         | 0.6   |
| Prednisolone           | 9         | 1.8   |
| Phenobarbitone         | 80        | 16.1  |
| Bisacodyl              | 1         | 0.2   |
| Sulfur                 | 1         | 0.2   |
| Spiroonolactone        | 2         | 0.4   |
| Tinidazole             | 1         | 0.2   |
| Gentamicin             | 7         | 1.4   |
| Crystalline Penicillin | 3         | 0.6   |
| Erythromycin           | 2         | 0.4   |
| Ciprofloxacin          | 1         | 0.2   |
| Diclofenac             | 1         | 0.2   |
| Mebendazole            | 3         | 0.6   |
| Augmentin              | 2         | 0.4   |
| Phenytoin              | 76        | 15.2  |
| Spiroonolactone        | 12        | 2.4   |
| KCl                    | 1         | 0.2   |
| Risperidone            | 2         | 0.4   |
| Sodium valproate       | 4         | 0.8   |
| Pyridoxine             | 1         | 0.2   |
| Propranolol            | 1         | 0.2   |
| Cotrimoxazole          | 2         | 0.4   |
| Mebendazole            | 3         | 0.6   |
| Enalapril              | 2         | 0.4   |
| Chlorpheniramine       | 1         | 0.2   |
| Digoxin                | 1         | 0.2   |
| ASA                    | 1         | 0.2   |
| Carbamazepine          | 1         | 0.2   |
| Total                  | 496       | 100.0 |

off-label medication ranging from 36.3% to 85%.<sup>24–27</sup> The disparities could be due to changes in the availability of pediatric-approved drugs, differing study designs, sample sizes, or pediatric medication use policies.

The findings of this study revealed that drugs for CNS diseases were the most commonly recommended pharmaceuticals for children in an off-label way (32.5%). These data are consistent with a study conducted in Pakistan, which found that CNS medicines were the most often administered off-label prescription (28.5%).<sup>27</sup> Phenobarbitone (16.1%)

was the most regularly administered off-label medication, followed by phenytoin (15.2%). However, this finding differs from a study conducted in Indonesian hospitals, which revealed that ranitidine is the most commonly prescribed off-label medication for children. These disparities could be attributable to distinct patient groups with various indications in different countries, but they could also be owing to varying definitions of off-label medication.<sup>28</sup>

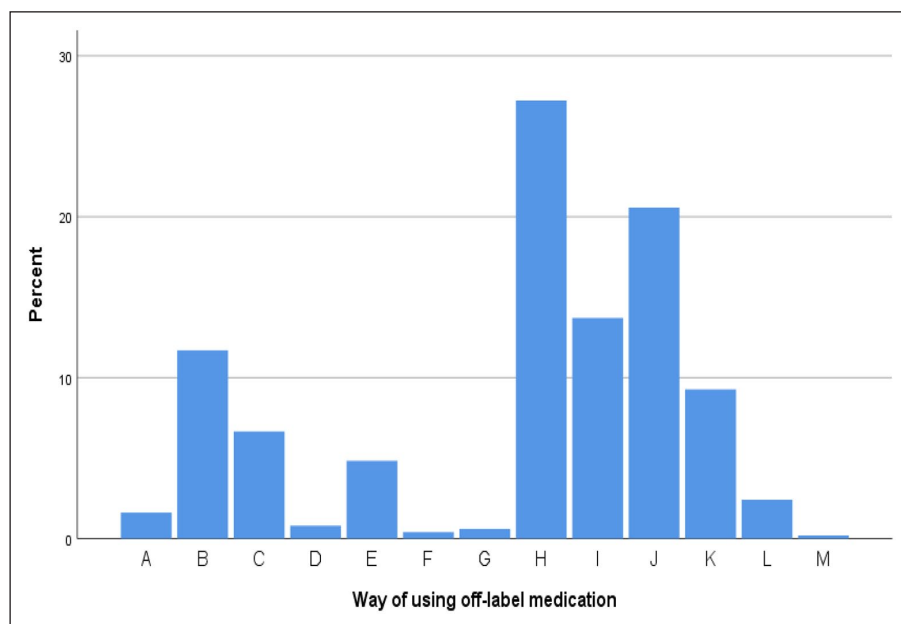
The majority of pediatric off-label medications were administered by splitting adult tablets into little portions to make them appropriate for children. As a result of the findings, numerous prescriptions contained off-label medications in overdose, tablet cutting, and adult tablet/capsule preparation in the form of solution and suspension. The findings are similar to those of a study conducted in Brazil, Indonesia, and France,<sup>23,28,29</sup> which found that off-label medications were used in the following ways: underdose, overdose, unapproved frequency and indication, unapproved dosage form by cutting the tablet and diluting with water, improper route of administration, and using contraindicated medications. This could be owing to a lack of pediatric medication and appropriate dosage forms. In comparison to other pediatric age groups, children aged 2 to 11 years were commonly exposed to off-label medications, according to this study. This finding is comparable to that of an Indonesian study.<sup>23</sup>

In this study, the lack of information on pediatric off-label medication was positively associated with off-label pediatric medication use. A lack of information regarding the risks of off-label medication may encourage health providers to prescribe and use off-label medications for children regularly. The absence of pediatric medication and lack of suitable pediatric dosage forms were also found to be positively associated with off-label pediatric prescribing when compared to non-use. In contrast to what has been documented by others, off-label pediatric medications were not connected with pediatric age, education level, or professional qualification in our investigation.<sup>3</sup>

Power analysis for sample size calculation was not done, and it was the limitation of the study. In addition to this, all demographic characteristics of health care workers were not included in the bivariable and multivariable regression analysis.

## Conclusion

Despite the numerous initiatives implemented to promote rational medication uses in children worldwide, this study reports a high prevalence of off-label prescribing in pediatric patients in a pediatric medical ward in a hospital setting in Ethiopia. Almost one of three drugs prescribed in the study area was off-label. Most notably, drugs for the treatment of CNS disorders such as phenobarbitone and phenytoin were the most commonly prescribed off-label medications. Lack of sufficient information about the risks of off-label



**Figure 2.** Ways of pediatric off-label medication use.

NB: C=Prescriptions that contain only under dose medication.

D=Prescriptions which contain medications with an improper route of administration.

E=Prescriptions which contain medications with improper Frequency.

F=Prescriptions which contain medications with improper Duration.

G=Prescriptions which contain medications with Contraindication.

H=Prescriptions which contain medications with Cutting adult tablet.

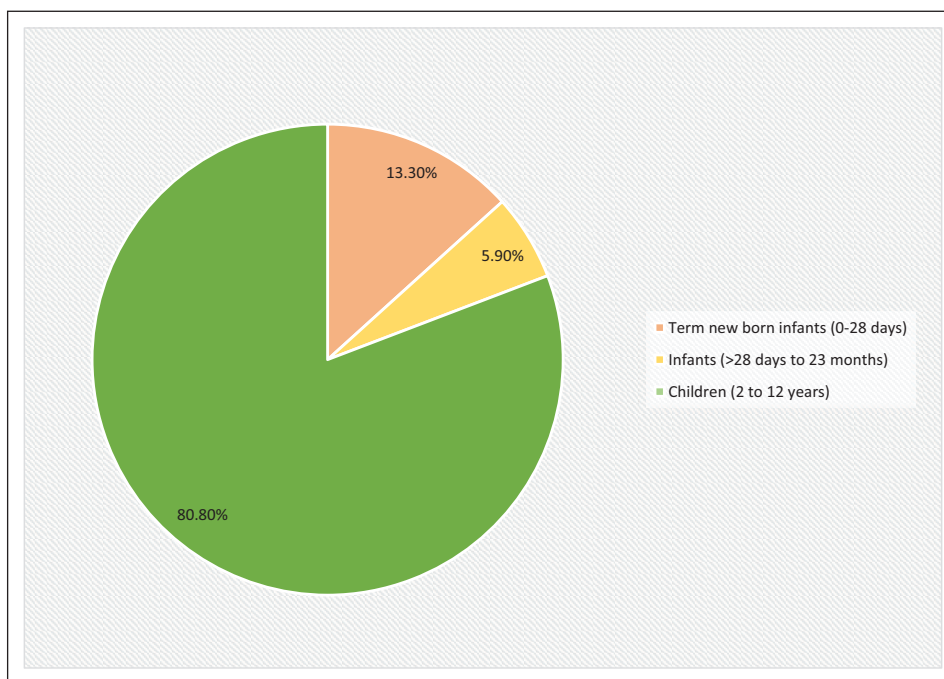
I=Prescriptions which contain medications by Formulating adult tablets in solution/ suspension.

J=Prescriptions which contain medications with overdose, cutting adult tablet and formulating suspension from tablet.

K=Prescriptions which contain medications both with Overdose and cutting tablet.

L=Prescriptions contain medications with Overdose, improper route of administration, cutting and formulating suspension.

M=Prescriptions which contain medications with Overdose and making adult tablet as solution or suspension.



**Figure 3.** Pediatrics age group classifications who exposed to off-label medications.

**Table 4.** Bivariable and multivariable logistic regression analyses to identify factors associated with pediatric off-label medication prevalence.

| Variables                                     |  | Bivariable analysis |         | Multivariable analysis |         |
|---|--|---------------------|---------|------------------------|---------|
|   |  | COR (95% CI)        | p-value | AOR (95% CI)           | p-value |
| Sex of professionals                          | Male                                   | 0.665 (0.231–1.920) | 0.451   | –                      | –       |
|   | Female                                 |                     |         |                        |         |
| Training                                      | No training                            | 2.412 (0.631–9.217) | 0.198   | –                      | –       |
|   | Get training                           |                     |         |                        |         |
| Information access about Off-label medication | Lack of information                    | 0.090 (0.06–0.128)  | < 0.001 | 11.968 (5.648–25.368)  | < 0.001 |
|   | Have information access                |                     |         |                        |         |
| Guideline availability                        | Lack of guideline                      | 1.487 (0.567–6.013) | 0.308   | –                      | –       |
|   | Have guideline                         |                     |         |                        |         |
| Formulary Availability                        | Lack of formulary                      | 1.624 (0.600–4.392) | 0.340   | –                      | –       |
|   | Have Formulary                         |                     |         |                        |         |
| Drug information center (DIC) availability    | No functional DIC                      | 0.704 (0.219–2.266) | 0.556   | –                      | –       |
|   | Have functional DIC                    |                     |         |                        |         |
| Pediatric drug availability                   | Shortage of pediatric drugs            | 0.083 (0.057–0.121) | 0.001   | 4.683 (2.113–10.379)   | < 0.001 |
|   | Have sufficient pediatric drugs        |                     |         |                        |         |
| Pediatric dosage form availability            | Shortage of pediatric dosage form      | 0.094 (0.065–0.136) | 0.000   | 46.725 (31.483–69.347) | < 0.001 |
|   | Have sufficient pediatric dosage forms |                     |         |                        |         |

AOR: adjusted odds ratio; CI: confidence interval; COR: crude odds ratio.

medication, shortage of pediatric medication, and suitable pediatric dosage forms were associated with the use of off-label pediatric medication compared to non-use. Due to the possible complications associated with off-label medications, health professionals should prescribe when only the benefit of this medication is certain and when patients have exhausted all other approved options, as may be the case with rare diseases. Further research should focus on the long-term effects associated with off-label medication use in pediatrics to assess whether the potential risks are balanced with the therapeutical benefit.

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### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Ethical approval

Ethical approval for this study was obtained from Debre Markos University, College of Health Sciences, ethical review committee (HSC/R/C/Ser/Co/210/11/13).

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### Informed consent

Written informed consent was obtained from all subjects before the study.

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### Supplemental material

Supplemental material for this article is available online.

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